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ISMELIN

Guanethidine (Ismelin - Ciba) is a new drug offered for the treatment of moderate to severe hypertension. A confident judgment on the drug must await the performance of controlled trials and longer clinical experience. Nevertheless, Ismelin appears to be of the same order of effectiveness as the ganglion-blocking drugs (see note on Veterans Administration study below), and it is free of many of the serious side effects of the ganglion blockers (D. W. Richardson and E. M. Wyso, Va. Med. Monthly, 86: 377, 1959). If present evidence as to effectiveness is confirmed and no new toxic or side effects appear with wide use, Ismelin may largely replace the ganglion blockers in hypertension therapy.

The chief disadvantage of both Ismelin and the ganglion blockers is the risk of orthostatic hypotension, sometimes with serious and even fatal consequences. The risk is especially great in patients with coronary, renal or cerebro-vascular disease. Therefore, all of these drugs must be used under close medical supervision, and none should be used except where the severity of the hypertensive disease warrants the risk. (See the Medical Letter review of Inversine, 1: 53, July 24, 1959, and of Ostensin, 2: 13, Feb. 19, 1960.)

SITE OF ACTION - Ismelin acts by inhibiting the release of norepinephrine at the sympathetic nerve endings. Like sympathectomy, it actually increases sensitivity to injected norepinephrine. It does not have the effect on parasympathetic nerve function which is responsible for the gastrointestinal and other unpleasant or disabling side effects of the ganglion blockers. The drug can, therefore, be used by many patients who are unable to tolerate the side effects of the ganglion blockers.

The effects of Ismelin are prolonged and cumulative. With large initial doses maximal effects generally appear in two or three days; with smaller doses several additional days may be required for maximal effect. When dosage is discontinued, the effects of the drug do not diminish appreciably for three or four days, and some effects may persist for as long as three weeks. The prolonged action and the good absorption of the drug permit easier control than with the ganglion blockers. Only a few instances of tolerance requiring increasing doses have been reported in published studies, though other instances have been noted by a Medical Letter consultant. Whether tolerance will prove to be a problem will be determined only by prolonged trial.

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SIDE EFFECTS - Diarrhea has been the most common complication with Ismelin, but it is seldom severe enough to interfere with continued therapy. Fatigue, muscle-aching, weakness and malaise have generally been encountered only with excessive doses. Unlike the ganglion blockers, Ismelin does not cause loss of erection, but it does in some cases inhibit ejaculation. A number of patients have developed unexplained edema and cardiac failure. Nausea, nasal stuffiness, ptosis, smarting of the eyes, and blurring of the vision may also occur. Though none of the published studies show allergic reactions, one Medical Letter consultant reports the occurrence of rashes in three patients taking Ismelin. Symptoms due to orthostatic hypotension (ranging from mild dizziness to syncope) are immediately relieved if the patient lies down; manifestations of transient cerebral ischemia have, however, been observed, and some reduction in renal function frequently occurs.

DOSAGE AND CONTROL - Since orthostatic hypotension imposes the major limitation on effective therapy, dosage with Ismelin must be controlled by frequent blood-pressure readings. Like the ganglion blockers, the drug tends to have marked effect on standing blood pressure, with relatively little effect on supine pressure; therefore readings should always include the standing position. The effect of Ismelin, as of the ganglion blockers, is greatest in the morning, with progressive rise in blood pressure during the day. Readings should, therefore, be taken soon after the patient arises; otherwise dangerous degrees of hypotension may go undetected. (The patient should be instructed to sit on the side of the bed for a few minutes when he first arises in the morning and then to stand by the bed for about a minute, lying down if he feels dizzy or faint.) The hypotensive effects of Ismelin can be counteracted with norepinephrine (Levophed) or metaraminol (Aramine), but not with methamphetamine (Methedrine), ephedrine or mephentermine (Wyamine) (I. H. Page and H. P. Dustan, JAMA, 170: 1265, 1959).

Ismelin is available in 10- and 25-mg. oral tablets. Some investigators have used large initial doses, but it is generally better practice, except in emergencies, to start with a dose of 12.5 mg. daily, increasing the dose at intervals of five to seven days until an adequate reduction of standing blood pressure is achieved. Dosage should be reduced or omitted if standing blood pressure drops excessively, or if supine pressure drops much below its usual level. For most patients, the maintenance requirement is 25 to 75 mg. per day in a single dose. As with the ganglion blockers, the use of the thiazides may reduce the required dosage of Ismelin. The cost of Ismelin is about $8 per hundred 10-mg. tablets and about $12 per hundred 25-mg. tablets.

VETERANS ADMINISTRATION STUDY OF ANTIHYPERTENSIVE DRUGS

The first results of a major cooperative study of antihypertensive drugs by eight Veterans Administration hospitals have now been published (AMA Arch. Int. Med., 106: 81, July 1960). This initial report deals with the comparative effectiveness of reserpine alone, hydralazine (Apresoline - Ciba) with reserpine, and reserpine with each of three ganglion-blocking drugs, chlorisondamine (Ecolid - Ciba), mecamylamine (Inversine - Merck), and pentolinium tartrate (Ansolysen - Wyeth). The study was exceptionally well-controlled, with a sufficient number

of patients to permit valid comparisons among treatment groups. The report is based on a study of 326 male hypertensive patients on continuous treatment with drugs or placebo, 232 of them for a full year, the rest for at least three months. The following paragraphs are from the summary and conclusions of the report:

"In mild hypertension, reserpine (0.5 mg. per day maintenance dose) plus hydralazine (200 mg. per day) was more effective than reserpine alone or placebos. Reserpine alone may have been slightly more effective than placebos but the difference was not statistically significant.

"In moderately severe hypertension, the reserpine plus hydralazine regimen was considerably more effective than either reserpine alone or placebos. The mean change in diastolic pressure was −13.7 mm. Hg with reserpine-hydralazine, −4.3 mm. with reserpine alone, and +0.9 mm. Hg with placebos. Reserpine plus hydralazine produced as great a reduction of blood pressure as reserpine plus ganglion blocking drugs in moderately severe hypertension.

"All three of the ganglionic blocking agents produced significant reductions of blood pressure [in severe hypertension]. The mean change from hospital control levels in 128 patients was −16.5/−13.9 mm. Hg. The range of response was wide, varying from rises of blood pressure in approximately 20% of patients to reductions of 40/30 mm. Hg in another 20%. There were no significant differences in antihypertensive effectiveness among mecamylamine, chlorisondamine, or pentolinium tartrate."

ORAL POLIO VACCINE

The announcement that the U.S. Public Health Service will permit the production of live poliovirus vaccine using the Sabin strains as soon as manufacturers are able to meet certain rigid safety requirements should not be allowed to discourage the present use of killed-virus vaccine. The government does not expect substantial quantities of the live-virus oral vaccine to be available before the spring or summer of 1961 at the earliest. Furthermore, not all problems relating to the use of the live virus vaccine have yet been resolved. The long delay in the decision to permit general use of live-virus vaccines resulted chiefly from the fear that the attenuated viruses would regain full virulence with passage through man. However, the Sabin vaccine, one of the three live-virus vaccines tested, is not known to have caused any illness. The risk of reversion is diminished when the vaccine is administered to entire communities within a short period, as has been done in most of the mass trials.

BLOCKING EFFECT - There can be little doubt that when infection by the live attenuated polioviruses occurs, a high degree of immunity is induced; but occasionally, the interfering effect of pre-existing infections caused by other enteric viruses blocks the immunizing poliovirus infection. Furthermore, when the three virus types are administered in a single dose, there may be a similar blocking action, and infection by only one or two types rather than all three may occur. In one Mexican trial in an area where infection with intestinal viruses was endemic, however, two doses of the combined Sabin vaccine produced im-

munity to all three types of poliovirus in 70 to 90 per cent of the subjects. Nevertheless, immunity to all three types can be obtained more uniformly if, in place of a combined vaccine, each type is given separately with an interval between doses (A. B. Sabin, AMA Arch. Int. Med., 106:5, 1960; H. Koprowski, British Med. J., July 9, 1960, p. 85). It is apparent that the optimal composition of the vaccine and the best mode of administering it have yet to be determined.

In Sweden it is planned to use the killed-virus vaccine during the child's first two years of life, and the oral vaccine subsequently. The strong likelihood that the combined use of the two vaccines, where feasible, will provide maximum protection makes continued use of killed-virus vaccine particularly desirable.

PURIVAX

Purivax (Merck) - a new injectable poliomyelitis vaccine - is a highly purified preparation of formalin-inactivated poliovirus. It is essentially free of monkey-kidney antigen, penicillin and streptomycin, but it does contain 50 mcg. of neomycin base per cc. Its purity minimizes the risk of allergic reactions and also permits accurate standardization by weight of virus. As a result of concentration during purification, a dose of 0.5 cc. - half the Salk vaccine dose - is adequate.

Purivax induces high antibody titers against all three types of poliovirus. Moreover, the highly virulent Mahoney strain of type I used in the Salk vaccine has been replaced by the less virulent Parker strain for greater safety. Two 0.5-cc. doses given one month apart effect antibody production to all three types of poliovirus in over 90 per cent of subjects - a much higher percentage than with the Salk vaccine. A third injection seven months or more after the second one is, however, recommended. Medical Letter consultants advise the routine use of Purivax in place of Salk vaccine despite the higher cost (about $1.50 per dose for Purivax; about 50¢ per dose for Salk vaccine).

KETOSTIX AND ACETEST TABLETS

Ketostix and Acetest tablets, both Ames products, provide simple and reliable tests for ketonuria. The Ketostix strips contain sodium nitroprusside, disodium phosphate and glycine. They are dipped in the urine sample, removed, and read exactly one minute later against a color chart representing mild, moderate and strong positive reactions. This test detects only acetoacetic acid, the major ketone body found in the urine.

Acetest tablets contain lactose in addition to the reagents found in the strips. A drop of ketone-positive urine placed on the tablet produces a color change which is read against a color chart after 30 seconds. This test detects acetone as well as acetoacetic acid. The tablets can also be used for a semi-quantitative test of serum ketones. A patient may have fairly marked acetonuria without significant amounts of acetone in the serum (as in post-operative starvation). Conversely, in diabetic acidosis, ketonuria may be mild to moderate despite marked ketonemia. Both tests have the advantage of convenience, and they are equal in sensitivity, reliability and quantitativeness to the older methods. The cost of 100 tablets is $1.60; 90 strips cost $2.40.

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